Methods Faulted in Fatal Gene Therapy
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Federal investigators have uncovered serious problems in the gene therapy experiment that killed a Tucson teenager in September, including new evidence that the young man should not have been allowed into the risky study because he was too sick at the time.

Jesse Gelsinger's liver was not functioning at the minimal level that regulators had required for inclusion in the study when University of Pennsylvania researchers infused trillions of genetically engineered viruses into the 18-year-old, Food and Drug Administration officials said.

Moreover, officials said, the researchers failed to notify the agency when two earlier volunteers in the experiment suffered side effects so severe that the study should have been put on immediate hold, according to rules established in advance by the scientists and the FDA.

The Penn researchers also did not tell federal regulators about the results of some crucial animal experiments that might have influenced the agency's judgment of the study's safety, officials said. Nor did the researchers tell the FDA about a key change in wording on the study's patient consent form, which ultimately left volunteers in the dark about the deaths of four monkeys that had undergone a similar treatment.

The new information is the first to emerge from an ongoing federal investigation into Gelsinger's death and raises fresh questions about the conduct of the scientists involved. It stands in stark contrast to a public statement released last week by the Penn team that attributed Gelsinger's death to the gene therapy but claimed that no "human error" had contributed to his demise.

More broadly, the discovery of so many apparent lapses at one of the nation's leading gene therapy centers deals a serious blow to an already beleaguered branch of experimental medicine, which for nine years has sought to cure cancer and other diseases by giving people new genes but has yet to achieve its first cure.

The field has come under increased scrutiny in the past two months after evidence emerged that researchers in New York and Boston had failed to tell the National Institutes of Health about several deaths and serious side effects in gene therapy patients, in violation of federal reporting rules.

On Thursday, the Penn team and the FDA are to present the preliminary results of their separate investigations into Gelsinger's death as part of a special three-day meeting beginning today at the NIH, at which biotechnology industry representatives have said they will call for reduced federal oversight of gene therapy experiments.

The Penn team, led by James M. Wilson and Steven E. Raper of Penn, and Mark L. Batshaw of Children's Hospital in Washington, declined to answer questions yesterday but released a written statement.

"We are disappointed by the FDA's release to certain media outlets of its preliminary findings about our gene therapy clinical trial . . . prior to either completing their report or communicating these findings to us," the team said. "Upon completion of the FDA's review, we are confident that a clearer understanding will emerge."

Gelsinger's father has said in the past that he did not blame the researchers for his son's death and that even if they had made mistakes, he still supported their efforts. He was en route to the NIH meeting yesterday and could not be reached for comment.

Although many patients have died from their underlying diseases while getting gene therapy, Gelsinger's death is believed to be the first directly caused by it. The experiment in which he participated aimed to treat ornithine transcarbamylase (OTC) deficiency, an inherited liver disease that causes life-threatening levels of ammonia to build up in the blood.

The experiment has stirred controversy since it was first proposed in 1995 because it calls for the infusion of high doses of a toxic virus into healthy volunteers or patients who, like Gelsinger, have their disease under control with conventional treatment.

The Washington Post reported last month that the researchers went ahead with the study despite evidence of serious side effects in animals and in at least one earlier volunteer. The story also disclosed that a company founded by Wilson had a financial interest in the study's success, a factor he has denied influenced the decision to forge ahead.

The FDA began investigating the Gelsinger case immediately after it learned of the Sept. 17 death, officials said, and the inquiry has gradually expanded since then. About a week ago, FDA officials visited the Penn campus, where a review of research records raised serious concerns, they said.

Most notably, investigators discovered that Gelsinger's blood had elevated ammonia levels, an indication that his liver was working even less efficiently than usual. Although the levels exceeded the maximum allowed for volunteers in the study, the scientists went ahead with the infusion of gene-altered viruses, FDA officials said.

Gelsinger's acceptance into the study is one of "a number of different areas that we have concerns about," said Kathryn Zoon, director of the FDA's Center for Biologics Evaluation and Research, which oversees gene therapy.

In their statement yesterday, the Penn team said Gelsinger's ammonia levels were within allowable limits when he was "enrolled." The FDA did not dispute that finding, but said the levels were no longer acceptable on the day Gelsinger was infused, which they said was the relevant measure.

FDA officials said it's difficult to know whether Gelsinger's weakened liver contributed to his death. The virus-based therapy is known to cause potentially life-threatening liver inflammation – one of the reasons that NIH reviewers had questioned the wisdom of trying the experiment on OTC patients. Because Gelsinger was one of the last volunteers to get into the study, he received the highest dose allowed.

Zoon said that at least two earlier volunteers who received lower doses than Gelsinger's suffered "Grade 3" liver damage, which required that researchers immediately halt the study and notify the FDA for a decision on whether they could proceed. But the FDA was not notified of those cases, Zoon said.

The study was designed so that doses were to be increased every three or four patients, but only if the FDA received assurances from researchers that those volunteers had done well.

Soon after Gelsinger's death, Wilson told The Post that no volunteers had suffered serious side effects except Gelsinger. Later, he acknowledged a single case of serious liver damage at a dose level two steps lower than the one Gelsinger got, but he did not mention the second incident that the FDA says it has documented at that same level.

Wilson also repeatedly said that at the next higher dose level – the one just below the one that Gelsinger got – none of the three volunteers had serious liver reactions. Tish Simon of Union, N.J., said in an interview yesterday that she was one of those three. She said a blood test two weeks after her infusion showed liver enzyme levels about five times the norm – a level that, according to the study protocol, demands at least FDA notification and possibly a halt to the study. Simon is apparently not among the two cases cited by the FDA.

She was called back four days later to Penn for repeat tests, which indicated the levels had dropped, she said.

The Penn team said yesterday it had provided the FDA with "comprehensive" data on patient toxicity.

Separately, Zoon said she was concerned that the informed consent form approved by the National Institutes of Health and FDA had noted that monkeys receiving a similar treatment had died, but the form that patients ultimately read and signed made no mention of those deaths – a discrepancy she said "we are very concerned about."

Zoon said the FDA does not have ultimate authority to approve the wording of consent forms; that responsibility belongs to review boards run by the institutions where the research is being done. Officials from Penn's review board did not respond to inquiries from The Post yesterday. A government investigation last year concluded that such boards are overworked and underfunded and are failing to adequately protect volunteers in medical experiments.